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10/581,468	05/04/2007	Balaji Balasa	116 US PC02	2007

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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,468	BALASA ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-35* is/are pending in the application.

4a) Of the above claim(s) *35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-34* is/are rejected.

7)☒ Claim(s) *24* is/are objected to.

8)☒ Claim(s) *24-35* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 August 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment to the claims of 8/11/09, and the amendment to the specification of 3/30/10, have each been entered in full. Claims 1-23 are canceled. New claims 24-35 are added. Claims 24-35 are pending in the instant application.

Claim 35 is hereby withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species of inflammatory bowel disease (ulcerative colitis), there being no allowable generic or linking claim.

Claims 24-34 are under consideration, as they read upon the elected species.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (2/17/09).

The objection to the Drawings at pg 2-3 is *withdrawn* in view of the Replacement Sheets filed on 8/11/09.

The objections to the specification at pg 3-5 are *withdrawn* in view of Applicants' amendments to the specification.

All rejections of claims 11-20, 22 and 23 at pg 5-14 are moot in view of Applicants' cancellation of these claims.

New objections and/or rejections necessitated by Applicants' amendment

Claim Objections

Claim 24 is objected to because of the following informalities:

In claim 24, the abbreviation "CDRs" should be accompanied by the full terminology the first time it is used in the claim (e.g., "...CDRs (complementarity determining regions)..." (see ¶ 18 of the published application).

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 is directed to an anti-IP-10 antibody that binds to "a protein encoded by SEQ ID NO: 1". However, in the Sequence Listing filed 8/26/09, SEQ ID NO: 1 is an amino acid sequence. It is unclear how an amino acid sequence (rather than a nucleic acid sequence) can encode a protein. Furthermore, SEQ ID NO: 1 represents only a single protein; therefore the article should be "the" instead of "a". This rejection would be rendered moot if the claim was amended to recite, for example, "the protein of SEQ ID NO: 1". For purposes of prosecution, the claim will be interpreted as if the claimed antibody binds to the protein of SEQ ID NO: 1 (IP-10).

Claim 24 is also indefinite because the recitation "and comprises a heavy chain variable region..." could be interpreted as either applying to the "antibody or antigen binding fragment" or to the "protein encoded by SEQ ID NO: 1". This rejection would be rendered moot if the claim was amended to recite, for example, "and wherein said antibody or antigen binding fragment comprises a heavy chain variable region..."

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method of reducing severity of at least one symptom of an inflammatory bowel disease in a subject in need thereof, comprising administering to said subject an effective amount of an isolated anti-IP-10 antibody or antibody fragment of claim 24

wherein said antibody or antigen binding fragment that binds to IP-10 also blocks the binding of IP-10 to the receptor CXCR3;

does not reasonably provide enablement for

A method of preventing or reducing severity of at least one symptom of an inflammatory bowel disease in a subject in need thereof, comprising administering to said subject an effective amount of an isolated anti-IP-10 antibody or antigen binding fragment of claim 24. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

This rejection is based on a portion of the previous enablement rejection that was previously set forth for the method of claims 17-20. Applicants have canceled said claims, and added new method claims 32-34, which necessitate application of this rejection to said claims.

Claims 32-34 are directed to a method of preventing or reducing severity of at least one symptom of an inflammatory bowel disease in a subject comprising administering an effective amount of an anti-IP-10 antibody or antigen binding fragment of claim 24. Independent claim 24 (not included in this rejection) is a product claim directed to an isolated anti-IP-10 antibody or antigen binding fragment. As set forth in the section titled, "Claim Rejections - 35 U.S.C. 112, 2nd Paragraph", claim 24 is indefinite because it recites that the antibody binds to a "protein encoded by SEQ ID NO: 1", yet SEQ ID NO: 1 is a protein. For purposes of prosecution, claim 24 has been interpreted as being directed to an antibody that binds to the protein of SEQ ID NO: 1. Claim 24 further requires that the claimed antibody includes a heavy chain variable

region comprising heavy chain CDRs of SEQ ID NO: 5, 6 and 74, and a light chain variable region comprising light chain CDRs of SEQ ID NO: 75, 76 and 77. The heavy chain CDRs are shown in Figure 1A as CDR1, CDR2 and CDR3 of the sequence labeled T55I (SEQ ID NO: 78). The light chain CDRs are shown in Figure 1B as CDR1, CDR2 and CDR3 of the sequence labeled HuAIP12 (SEQ ID NO: 46).

The specification teaches that SEQ ID NO: 46 is a VL sequence from the humanized antibody HuAIP12, which in turn was derived from the mouse monoclonal antibody AIP12, which binds to the human chemokine IP-10 (also known as CXCL10). The specification teaches that SEQ ID NO: 78 is a modified VH sequence derived from HuAIP12, with a single amino acid change at residue 55 (threonine to isoleucine). This change was based on a difference in the sequence of the VH of HuAIP12 and the VH of HuAIP13, a humanized antibody derived from the mouse monoclonal antibody AIP13, which also binds IP-10. The specification teaches that "[t]he removal of a threonine residue by substitution with isoleucine at position 55 in the VH unexpectedly increased the affinity of HuAIP12 to human IP-10. In example 9, the specification teaches that "[a]s shown in FIG. 2, HuAIP12 T55I inhibited IP-10-mediated chemotaxis of Ba/F3-CXCR3 cells more efficiently than HuAIP12, indicating that HuAIP12 T55I, which has a higher affinity to human IP-10 than HuAIP12, neutralizes the function of IP-10 more strongly than HuAIP12" (pg 49, lines 17-20).

The specification teaches that the term "antibody" (¶ 16 of the published application) refers to a protein "consisting of one or more polypeptides substantially encoded by immunoglobulin genes" including the "kappa, lambda, alpha, gamma (IgG, IgG_2, IgG_3, IgG_4), delta, epsilon and mu constant region genes, as well as the myriad immunoglobulin variable V region genes (as indicated below, there are V genes for both H-heavy- and L-light-chains)".

The specification and prior art enables the skilled artisan to make and screen antibody variants comprising the complete recited VH (SEQ ID NO: 78) and VL (SEQ ID NO: 46) regions and identify those that retain binding to the chemokine IP-10, as required by the claims. Furthermore, it was well known in the relevant art prior to the time of filing of the instant application that the heavy and light polypeptide chains each

contribute three CDRs to the antigen binding region of the antibody molecule. Furthermore, the prior art taught humanization of antibodies by transfer of the 6 CDRs from a donor framework region to an acceptor framework region and retention of antigen binding (Queen et al, 1989. PNAS. 86: 10029-10033; Riechmann et al, 1988. Nature. 332: 323-327). In light of the prior art disclosing the CDRs as being the essential structure of the antibody's binding site, the identification of the specific CDR sequence in the specification provides enough structure to define the antibody's binding site. In addition, the prior art for humanization supports obtaining successful antigen binding by transferring the 6 CDRs from a donor framework to an acceptor framework. Thus, it would not have been undue experimentation to obtain an antibody that would bind IP-10 and comprise the 6 CDRs as specifically defined in the claims at the time of filing. Therefore, the isolated anti-IP-10 antibody or antigen binding fragment of claim 1 that binds to a protein of SEQ ID NO: 1 (IP-10) and comprises a heavy chain variable region comprising heavy chain CDRs of SEQ ID NO: 5, 6 and 74, and a light chain variable region comprising light chain CDRs of SEQ ID NO: 75, 76 and 77, meets the requirements under 35 U.S.C. 112, first paragraph, for enablement. Thus, claims 24-31 are not included in this rejection.

However (as set forth previously for now canceled claims 17-20), claims 32-34 are directed to a method of preventing or reducing severity of at least one symptom of an inflammatory bowel disease in a subject in need thereof, comprising administering to said subject an effective amount of an antibody or antibody binding fragment according to claim 24. Prior to Applicants' earliest priority date (12/4/03), Singh et al (2003. Journal of Immunology. 171: 1401-1406; cited previously) taught that "[f]or the first time, we demonstrate that Ab therapy directed toward IP-10 is successful at impeding IBD development" (pg 1401) and "our studies both highlight the importance of IP-10-CXCR3 interactions in CD and present a new target for immunotherapy for the treatment of colitis" (pg 1405). The relevant art further teaches that a fully human anti-IP-10 antibody has entered Phase I clinical trials for the treatment of ulcerative colitis (UC) (Kuhne et al. 2007. Journal of Immunology. 178: 131; 2 pages as printed; cited previously). Kuhne teaches that IP-10 (CXCL10) is "a chemotactic cytokine for activated T cells and

monocytes and plays an important role in migration of cells into sites of inflammation. The receptor for CXCL10, CXCR3, is expressed by activated T cells, eosinophils, NK, and endothelial cells. CXCL10 levels are elevated in ulcerative colitis (UC) amongst other inflammatory diseases. In preclinical animal models of UC, antibodies against CXCL10 have been shown to modify disease progression". These teachings highlight that, in addition to requiring that the antibody binds to IP-10, antibodies to be used in the claimed treatment method require an additional function: the ability to block the binding of IP-10 to the receptor CXCR3. Depending on the structure, a modified antibody that binds to IP-10 will not necessarily also inhibit binding of IP-10 to the receptor CXCR3. The specification provides a chemotaxis assay for determining whether or not an anti-IP-10 antibody also inhibits binding of IP-10 to the receptor. As described in Example 9, the ability of an antibody "to block the function of IP-10 was measured by a chemotaxis assay using a stable transfectant to a murine hematopoietic cell line Ba/F3 expressing human CXCR3" (pg 49). However, while the antibodies and fragments to be used in the method of claim 32 are limited to those that bind to IP-10, they are not limited to those that can inhibit binding of IP-10 to the CXCR3 receptor. The instant specification does not provide any guidance on how antibodies that bind IP-10, yet fail to inhibit receptor binding, could be used to treat inflammatory bowel disease. In the absence of such guidance, it would require undue experimentation to identify a way that such antibodies could be used in the claimed treatment method.

Furthermore (as set forth previously for now canceled claims 17-20), the specification and prior art do not provide enablement for the full scope of treatment encompassed by claim 32 and dependent claims 33 and 34. Specifically, the claims are directed to "preventing or reducing severity of at least one symptom of inflammatory disease". While reducing the severity of at least one symptom of inflammatory bowel disease (IBD) is enabled by the teachings of the specification and the relevant art with respect to an anti-IP10 antibody that blocks IP-10 binding to CXCR3, preventing at least one symptom of IBD is not enabled. Enablement of "prevention" requires support for administration of an agent before symptoms appear, and should result in some reduction of occurrence. A disclosure of treatment of symptomatic patients alone does

not support a claim to prevention in healthy, or asymptomatic, patients. In the instant case, the relevant art provides support only for reduction in severity rather than occurrence. As shown in Table II of Singh et al (2003; cited above), "Anti-IP-10 Ab" treated mice still developed some colitis (colitis score ~2.13), which while reduced compared to untreated mice (colitis score ~6.89), was still higher than that of wild type mice without colitis. This is supported by Suzuki et al (2007. Pathology International. 57: 413-420; cited previously), in which a different model of murine colitis was tested for treatment with anti-IP-10. As shown in Figure 2, treatment with anti-IP-10 reduced infiltrating cells in colitis but did not restore them to wild type levels. Further, in each study, the anti-IP-10 antibody was administered after development of colitis. The instant specification provides no working examples wherein a symptom of inflammatory bowel disease is prevented. In view of the teachings of the relevant art, and the lack of guidance in the instant specification, it would require undue experimentation to identify a way that such antibodies could be used in the claimed treatment method.

In the 8/11/09 response, Applicants have cancelled all of the claims previously rejected under 35 U.S.C. § 112, first paragraph, and introduced new claims. The rejection set forth previously has been applied to new claims 32-34. Applicants' response to the rejection is addressed in so far as it applies to the new rejection.

Applicants' arguments (8/11/09; pg 13) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that the new claims are directed to an isolated anti-IP-10 antibody or antigen binding fragment that binds to a protein of SEQ ID NO: 1 (human IP-10) and comprises a heavy chain variable region comprising heavy chain CDRs of SEQ ID NO: 5, 6 and 74, and a light chain variable region comprising light chain CDRs of SEQ ID NO: 75, 76 and 77. Therefore, Applicants argue, that "the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement, has been obviated and should be withdrawn" (pg 13).

Applicants' arguments have been fully considered but are not found persuasive. The amendments to independent claim 24 have resulted in withdrawal of the rejection of

product claims 24-31 for lack of enablement under 35 U.S.C. § 112, first paragraph. However, dependent method claims 32-34 still lack enablement for the full scope of the claims for reasons set forth previously (for claims 17-20) and reiterated above.

Conclusion

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Bridget E Bunner/
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